REMARKS/ARGUMENTS

Claims 27 to 31, 33, 34, 36 to 46, 48, 49, 51 to 55, 57, 58, 60 to 62, 64 and 65, 81 and 82 have been cancelled by this amendment. Claim 75 has been amended, and claims 83 – 87 have been added.

The sole retained independent method claim (claim 75) is directed to *in vitro* methods of diagnosing infection in a human with a mycobacterium which expresses ESAT-6, e.g. *M. tuberculosis* infection, employing a specific panel of ESAT-6 peptides. Since the Examiner has suggested that the language " peptide represented by SEQ. ID. No." does not clearly define a precise sequence, claim 75 is now amended to define the relevant peptide panel as " consisting of the peptides of SEQ. ID nos.1 to 8". Claim 76 covers supplementation of this panel by inclusion of one or more of 3 additional specified peptide fragments of ESAT-6.

New claims 83 and 84 are identical to claims 78 and 79 apart from change of dependency to claim 76.

New claims 85 and 86 correspond to original claims 81 and 82 with change of dependency.

New kit claim 87 replaces cancelled kit claims 45 and 46 referring to peptide panels.

Argument against rejection under 35 U.S. C.102 (e) on Andersen et al

It is respectfully submitted that in maintaining rejection under 35. U.S. C. 102(e), the Examiner is taking a far too simplistic view of the requirements for arrival at the claimed invention and over-looking pertinent significant deficiencies in the teaching of the Andersen et al. Patent (US 5955077). It is refuted that the Andersen et al. Patent either explicitly or implicitly teaches clinical utility as regards humans of a diagnostic method employing a peptide panel as now claimed. It is not disputed that Andersen et al. did disclose diagnostic utility of ESAT-6 and did speculate that subsequences of ESAT-6 might be similarly employed. However, there is no data in the Andersen et al. Patent to support clinical utility in respect of humans of a specific panel of small peptide fragments as now claimed.

The inventors in this instance set out to establish whether a diagnostic test having clinical utility was feasible based on short T cell epitope-containing ESAT-6 fragments. This was a significant and complex undertaking for which the Andersen et al. disclosure provided no technical teaching of assistance whatsoever other than provision of the ESAT-6 protein sequence. It did little more than confirm that whole

ESAT-6 will produce a T cell response when utilized in a skin test in guinea pigs. This is long way from identification of a specific panel of peptides as now claimed for *in vitro* human diagnosis, and does not even support that such a panel with clinical diagnostic utility is an achievable end-point.

As a starting point, it needs to be borne in mind that T cell epitopes are recognized in humans in the context of human leucocyte antigen (HLA) molecules. It was not evident at the outset that ALL HLA SPECIFICITIES PREDOMINATING IN THE HUMAN POPULATION would be represented by at least one member of a peptide panel as now specified in the claims. That this is indeed the case is supported by data in the subject specification, which confirms that the panel of just 8 short peptide fragments of ESAT-6 listed in claim 1 correctly identified 96% of tuberculosis patients tested with elimination of the problem of false positives arising from BCG vaccination (a recognized problem with the conventional tuberculin skin test for tuberculosis).

Arrival at the invention as now claimed demanded:

(a) assembling a large number of human patients for clinical trials and defining the TB status and disease classification for each using conventional diagnostics and skilled clinical assessment- because there was no gold standard test for determining TB status, it was necessary to compare the peptide test results with conventional analysis, i.e. using multiple and complementary diagnostic approaches;

(b) identifying T cell epitopes that were specific for different HLA specificities which exist across the human population in an attempt to provide the necessary breadth of coverage of all predominant HLA specificities (as indicated above such necessary breadth of targeting of a peptide panel to facilitate a universal assay for use with T cells derived from a broad spectrum of patients was not predictable from the work of Andersen et al.)

(c) establishing whether a particular peptide panel combination would yield a test having sufficiently high sensitivity and specificity to support a clinical test having superior accuracy to the existing skin test.

Accordingly, we contend that the inventors have gone well beyond the mere discovery of T cell epitopes in ESAT-6. They have identified peptide sequences that are diagnostically the most relevant, taking account of the differences between individuals within the human population from both clinical and immunological standpoints. Thus, we submit that the essential inventive step in this case consists

of the identification of important ESAT-6 T cell epitopes IN THE CONTEXT OF THIS COMBINED CLINICAL AND IMMUNOLOGICAL SETTING, and the surprising showing that a panel comprising a small, convenient number of these ESAT-6 peptides does in fact provide the basis for a 'universal' test for TB which outperforms existing tests in terms of accuracy.

Thus, it is refuted that the Andersen et al. Patent specification put a person skilled in the art in possession of the invention as claimed. It is submitted that the work of the inventors is separately inventive over the disclosure of the Andersen et al. Patent. In further support of this, reference is made once more to Elhay et al. Infect. Immun. (July 1988) 66, 3454-3456 (deriving from the same research group as the Andersen et al. Patent). It is the case that use of peptides as compared to whole protein in diagnostic assays may be preferred for a number of reasons including cost saving in kit production. It is therefore indeed highly notable that even more than 3 years after publication of WO 95/01441 (corresponding to the Andersen et al. US Patent), as evident from the Elhay et al. paper, Andersen et al. were not advocating any panel of ESAT-6 fragments for diagnostic use in humans. The Elhay et al paper provides data showing that a peptide from the C-terminal region of ESAT-6, peptide p8, is effective in a skin test in detecting T cells in guinea pigs infected with *M. tuberculosis.* This is irrelevant to establishment of a clinically useful *in vitro* diagnostic assay as now claimed for use with human T cell samples without restriction on HLA specificity. It is simply not possible to extrapolate from any prior art animal studies that any particular fragment, or combination of fragments, of ESAT-6 will be a useful diagnostic tool in humans. It is highlighted once again that even at the publication date of the Elhay et al. paper Andersen et al. were suggesting that a good diagnostic reagent for use with humans would be a combination of whole ESAT-6 with another whole protein. If anything, Andersen et al. were thus directing away from the claimed invention close to the priority date.

No prior art document available to the Examiner discloses or directs provision of a selection of ESAT-6 fragments as now claimed in the context of a highly advantageous and clinically useful diagnostic test for *M. tuberculosis* infection in humans. The work of the inventors in establishing the clinical utility of T cell epitope-containing peptide panels as now claimed for *in vitro* human diagnosis represented a significant, non-predictable advance in the diagnosis of tuberculosis, which now underpins kits being marketed for a new human TB test. This test is increasingly

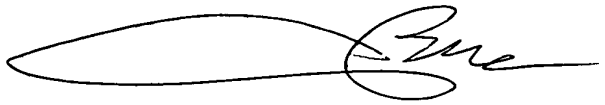
being used by diagnostic laboratories to replace the conventional skin test in view of its high degree of accuracy.

In view of the amendments and foregoing remarks it is believed that the application is now in condition for allowance and respectfully solicits a Notice of Allowance.

In the event all the claims are not allowed, entry of the foregoing amendment is requested as placing the application in better condition for appeal. In addition, in such case, the examiner is requested to telephone applicant's attorney at the number below if such a call would facilitate reaching allowed claims.

The Commissioner is hereby authorized to charge payment of any fees required associated with this communication or credit any overpayment to Deposit Account No. 50-0337. If an extension of time is required, please consider this a petition therefor and charge any additional fees which may be required to Deposit Account No. 50-0337. A duplicate copy of this page is enclosed.

Respectfully submitted,



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